Generation of Vascular Endothelial Cells and Hematopoietic Cells by Blastocyst Complementation.

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Public Summary:
One way to alleviate the current shortage in donor organs is to generate human organs within animals by a process called blastocyst complementation. However, organs are complex tissues that include blood vessels. Contamination of animal-derived blood vessels in the human organ could result in rejection following transplantation. Here, we have studied a new way to generate rejection-free transplantable organs by blocking blood vessel formation within the host, by genetically deleting a gene called Flk-1.

Scientific Abstract:
In the case of organ transplantation accompanied by vascular anastomosis, major histocompatibility complex mismatched vascular endothelial cells become a target for graft rejection. Production of a rejection-free, transplantable organ, therefore, requires simultaneous generation of vascular endothelial cells within the organ. To generate pluripotent stem cell (PSC)-derived vascular endothelial cells, we performed blastocyst complementation with a vascular endothelial growth factor receptor-2 homozygous mutant blastocyst. This mutation is embryonic lethal at embryonic (E) day 8.5-9.5 due to an early defect in endothelial and hematopoietic cells. The Flk-1 homozygous knockout chimeric mice survived to adulthood for over 1 year without any abnormality, and all vascular endothelial cells and hematopoietic cells were derived from the injected PSCs. This approach could be used in conjunction with other gene knockouts which induce organ deficiency to produce a rejection-free, transplantable organ in which all the organ's cells and vasculature are PSC derived.